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Mark B. Wilson Fulbright & Jaworski L.L.P. 600 Congress Avenue, Suite 2400 Austin, TX 78701			EPPERSON, JON D	
			ART UNIT	PAPER NUMBER
			1639	10

DATE MAILED: 10/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b> <i>File Copy</i>	Application No.	Applicant(s)		
	09/845,006	SCHINDLER, HANSGEORG		
Period for Reply	Examiner	Art Unit		
	Jon D Epperson	1639		
-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --				
<p>A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE <u>3</u> MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.</p> <ul style="list-style-type: none"> <li>- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.</li> <li>- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.</li> <li>- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.</li> <li>- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).</li> <li>- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).</li> </ul>				
<p><b>Status</b></p> <p>1)<input checked="" type="checkbox"/> Responsive to communication(s) filed on <u>11 August 2003</u>.</p> <p>2a)<input type="checkbox"/> This action is FINAL.                            2b)<input checked="" type="checkbox"/> This action is non-final.</p> <p>3)<input type="checkbox"/> Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under <i>Ex parte Quayle</i>, 1935 C.D. 11, 453 O.G. 213.</p>				
<p><b>Disposition of Claims</b></p> <p>4)<input checked="" type="checkbox"/> Claim(s) <u>24-60</u> is/are pending in the application.</p> <p>4a) Of the above claim(s) <u>41,43 and 46-60</u> is/are withdrawn from consideration.</p> <p>5)<input type="checkbox"/> Claim(s) _____ is/are allowed.</p> <p>6)<input checked="" type="checkbox"/> Claim(s) <u>24-40,42,44 and 45</u> is/are rejected.</p> <p>7)<input type="checkbox"/> Claim(s) _____ is/are objected to.</p> <p>8)<input type="checkbox"/> Claim(s) _____ are subject to restriction and/or election requirement.</p>				
<p><b>Application Papers</b></p> <p>9)<input type="checkbox"/> The specification is objected to by the Examiner.</p> <p>10)<input type="checkbox"/> The drawing(s) filed on _____ is/are: a)<input type="checkbox"/> accepted or b)<input type="checkbox"/> objected to by the Examiner. Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).</p> <p>11)<input type="checkbox"/> The proposed drawing correction filed on _____ is: a)<input type="checkbox"/> approved b)<input type="checkbox"/> disapproved by the Examiner. If approved, corrected drawings are required in reply to this Office action.</p> <p>12)<input type="checkbox"/> The oath or declaration is objected to by the Examiner.</p>				
<p><b>Priority under 35 U.S.C. §§ 119 and 120</b></p> <p>13)<input checked="" type="checkbox"/> Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f). a)<input type="checkbox"/> All    b)<input type="checkbox"/> Some *    c)<input checked="" type="checkbox"/> None of: 1.<input checked="" type="checkbox"/> Certified copies of the priority documents have been received. 2.<input type="checkbox"/> Certified copies of the priority documents have been received in Application No. _____. 3.<input type="checkbox"/> Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)). * See the attached detailed Office action for a list of the certified copies not received.</p>				
<p>14)<input type="checkbox"/> Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application). a)<input type="checkbox"/> The translation of the foreign language provisional application has been received.</p> <p>15)<input type="checkbox"/> Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.</p>				
<p><b>Attachment(s)</b></p> <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none;">           1)<input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            2)<input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)            3)<input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>6</u> </td> <td style="width: 50%; border: none;">           4)<input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____.            5)<input type="checkbox"/> Notice of Informal Patent Application (PTO-152)            6)<input type="checkbox"/> Other: _____         </td> </tr> </table>			1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>6</u>	4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____. 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) 6) <input type="checkbox"/> Other: _____
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## **DETAILED ACTION**

### *Status of the Application*

1. Receipt is acknowledged of a Response to a Restriction Requirement, which was dated on August, 11 2003 (Paper No. 9).

### *Priority Claims*

2. Acknowledgment is made of applicant's claim for foreign priority based on AUSTRIA A 1799/98 filed on October 28, 1998. It is noted, however, that Applicant has not filed a certified copy of the 1799/98 application as required by 35 U.S.C. 119(b) or PCT Rule 17. Therefore, the filing date of the instant application is deemed to be the filing date of PCT/AT99/00257 i.e.,

**October 28, 1999.**

### *Status of the Claims*

3. Claims 24-60 are pending in the present application.
4. Applicant's response to the Restriction and/or Election of Species requirements in Paper No. 9 is acknowledged (Applicant elected Group I, claims 24-45) and claims 46-60 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim (see below i.e., Response to Restriction and/or Election of Species). Please note: there was a typographical error in the original Restriction Requirement (i.e., Paper No. 8). Group I should include claims 24-45 (not

24-44 as stated in Paper No. 8, paragraph 1) and Group II should include the claims 46-60 (not claims 46-55 as stated in Paper No. 8, paragraph 1).

5. Please note: Applicant's elected species (dye laser, epifluorescence microscope, , normal sample holding means, xy drive and software, microtiter) were found in the art (HSAM cells, DMPE-Cys5) were not found, see rejections below. Applicant is reminded of MPEP § 803.02 with respect to species elections:

On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a nonelected species, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration. *The prior art search, however, will not be extended unnecessarily to cover all nonelected species.* Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-type claim will be reexamined. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim. In the event prior art is found during the reexamination that anticipates or renders obvious the amended Markush-type claim, the claim will be rejected and the action made final. Amendments submitted after the final rejection further restricting the scope of the claim may be denied entry.

6. Claims 41, 43 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected species, the requirement having been traversed in Paper No. 9 (see below i.e., **Response to Restriction and/or Election of Species**). The “molecule library” in claim 41 does not read on Applicant's elected “cells” and the “flowthrough cell” does not read on Applicant's “normal” sample holding means.

7. Therefore, claims 24-40, 42 and 44-45 are examined on the merits in this action.

***Response to Restriction and/or Election of Species***

8. Applicant's election of Group I (claims 22-45) with traverse in Paper No. 9 is acknowledged.

9. The traversal is on the ground(s) that "the arrangement as claimed specifically recites the use of single dye tracing (SDT) to monitor the molecule. Therefore, the Examiner's statement that different physical methods e.g., X-ray, NMR, mass-spec, electrochemical, etc. could be used to monitor the molecule is not valid. Furthermore, the Applicant points out that the Examiner would not have a serious burden of conducting a patentability search since the claimed arrangement and the claimed tracing methods both relate to SDT and are not distinct inventions" (see Paper No. 9, page 2, paragraph 2).

10. These arguments were fully considered but were not found persuasive. As stated in the Restriction Requirement dated July 2, 2003 (Paper No. 8), these inventions (Groups I-II) have acquired a separate status in the art as shown by their different classification and/or divergent subject matter. The different methods and/or products would require completely different searches in both the patent and non-patent databases, and there is no expectation that the searches would be coextensive. Therefore, this does create an undue search burden for the Office.

In addition, Applicants argument that the Examiner's statement that different physical methods e.g., X-ray, NMR, mass-spec, electrochemical, etc. could be used to monitor the molecule is not valid because the arrangement specifically recites the use of single dye tracing which would presumably preclude the use of these other techniques is not found persuasive. The Examiner contends that Applicants have impermissibly tried to claim two statutory classes of

inventions (i.e., an Apparatus and a product, see 35 U.S.C. § 101 rejection, below) and, as a result, the Examiner only needs to show that the “product” i.e., the sample in this case (e.g., the biological cells) can be used with another materially different method of using that product e.g., X-ray, NMR, etc. which has been adequately set forth in the original restriction (e.g., see Paper No. 8, paragraph 3).

In addition, even if *assuming arguendo* that Applicants could combine more than one statutory class of inventions any or all of the techniques (e.g., X-ray, NMR, mass-spec) could be combined with the fluorescence measurements leading to the same conclusion that the “product” i.e., the “apparatus-sample product” hybrid could still be practiced with a materially different method (e.g., see page 39, paragraph 2, showing “combination” with an electrophysiology method; please note could also be combined with X-ray, NMR, mass-spec methods as well).

11. Applicant’s election of species in Paper No. 9 is also acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election of species has also been treated as an election without traverse (MPEP § 818.03(a) and/or 37 CFR 1.111(b)).

12. As a result, the restriction requirement and/or election of species is still deemed proper and is therefore made FINAL.

#### ***Information Disclosure Statement***

13. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98 (b) requires a list of all patents, publications, or other information

submitted for consideration by the Office, and MPEP § 609 A(1) states, “the list may not be incorporated into the specification but must be submitted in a separate paper.” Therefore, unless the references have been cited by the examiner on the form PTO-892, they have not been considered.

14. The references listed on applicant’s PTO-1449 form have been considered by the Examiner. A copy of the form is attached to this Office Action.

*Specification*

15. The abstract of the disclosure is objected to because it is not one paragraph. Correction is required. See MPEP § 608.01(b). In addition, the abstract of the disclosure is objected to because it contains more than 150 words. (See MPEP § 608.01, “Abstract of the Disclosure: A brief narrative of the disclosure as a whole in a single paragraph of 150 words or less commencing on a separate sheet following the claims”).

16. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

17. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant’s cooperation is requested in correcting any errors of which applicant may become aware in the specification.

***Objections to the Claims***

18. Claim(s) 29 is/are objected to because of the following informalities:

A. Claim(s) 28 is missing a verb i.e., should read “said sample holding means is controlled”

***Claims Rejections - 35 U.S.C. 101***

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

19. Claims 24-40, 42 and 44-45 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims 22-45 are drawn to an “arrangement for visualizing molecules” that consists of both an “apparatus” i.e., the fluorescence detector (e.g., see dependent claim 37 disclosing an epifluorescence microscope apparatus) and a “product” i.e., the sample that is detected by the apparatus (e.g., see dependent claim 25 disclosing product “biological cells” that are placed within the apparatus), rather than a single statutory class of invention (i.e., Applicants are trying to claim both the apparatus and the products that are measured by the apparatus simultaneously which is not permissible).

The Examiner concedes that there are situations where claims are permissively drafted to include a reference to more than one statutory class of invention (e.g., see MPEP § 2173.05(p) disclosing “product-by-process” claims), but the Examiner notes that those situations are only permissible because Applicants make clear that the “product” and NOT the “process” is being

claimed (e.g., see MPEP § 2173.05(p), “A claim to a device, apparatus, manufacture, or composition of matter may contain a reference to the process in which it is intended to be used without being objectionable under 35 U.S.C. 112, second paragraph, so long as it is clear that the claim is directed to the product and not the process”) (emphasis added). Here, it is not clear whether Applicants intent to claim an “apparatus”, a “product” or a new statutory “hybrid” class consisting of an “apparatus and a product” (see 35 U.S.C. § 112, second paragraph). To the extent that Applicants are claiming a new “hybrid” statutory class of invention i.e., “apparatus-product” claims, the claims are rejected under 35 U.S.C. § 101.

***Claims Rejections - 35 U.S.C. 112, second paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

20. Claims 24-40, 42 and 44-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. For **claim 24**, is indefinite because it is not clear whether Applicants are trying to claim more than one statutory class of invention (i.e., apparatus and product) simultaneously? If Applicants are claiming only one statutory class of invention then the Examiner contends that it is not clear whether Applicants are claiming an “apparatus” or a “product”? For example, the epifluorescence microscope (e.g., see dependent claim 37) would appear to be an apparatus. However, the “biological cells” (e.g., see dependent

claim 25) would appear to be a product. Applicants are requested to clarify i.e., what statutory class of invention are you claiming i.e., a “product”, an “apparatus” or a “product-apparatus”? Therefore, claims 24 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

Please note that other “statutory hybrid” claims are not rejected like product-by-process claims (which is also being claimed here i.e., see claim 24, “using the single dye tracing (SDT) method”) because Applicants make clear what is being claimed i.e., the product (see MPEP § 2173.05(p), “A claim to a device, apparatus, manufacture, or composition of matter may contain a reference to the process in which it is intended to be used without being objectionable under 35 U.S.C. 112, second paragraph, so long as it is clear that the claim is directed to the product and not the process” i.e., the claim must make clear which statutory class of invention is being claimed) (emphasis added). That is not the case here. Applicants have not made clear whether the “apparatus” or the “product” is being claimed (see above).

B. *Claim 24* recites “large-area” fluorescence excitation. The term “large” is a relative term, which renders the claim indefinite and/or unclear. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. See also MPEP § 2173.05(b). The Examiner notes that Applicants do make the statement that “Due to the large-area fluorescence excitation, preferably 100 to 10,000  $\mu\text{m}^2$ , depending on the application, imaging of the excited molecules may be very rapid” (i.e., see page 7, paragraph 2). However, this statement does not make clear

whether Applicants intent the range 100 to 10,000  $\mu\text{m}^2$  to be a definition (i.e., limiting in nature) or merely an example (i.e., non-limiting in nature) for the “large-area” term. Furthermore, it is not clear in either to what extent the term “large” could extend beyond this limit i.e., it is not clear whether “areas” outside this range would infringe the claims (e.g., would 90  $\mu\text{m}^2$  infringe, 80  $\mu\text{m}^2$  infringe, etc). Consequently, the metes and bounds of the claimed invention cannot be determined.

C. **Claim 24** recites “highly sensitive” in line 1. The term “highly sensitive” is a relative term, which renders the claim indefinite and/or unclear. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. See also MPEP § 2173.05(b).

D. **Claim 24** recites the limitation “the sample holding means” and “said sample holding means.” There is insufficient antecedent basis for these limitations in the claim. Therefore, claim 24 and all dependent claims are rejected under 35 USC 112, second paragraph.

E. **Claim 24** recites the limitation “the detection and analysis system.” There is insufficient antecedent basis for this limitation in the claim. Therefore, claim 24 and all dependent claims are rejected under 35 USC 112, second paragraph.

F. For **claim 24**, the phrase “a control unit for coordinating … movements of at least one of said sample and said sample holding means with said sample” is vague and indefinite. For example, it is not clear whether how the movements of a sample could be coordinated with respect to itself i.e., “movements of at least one of said sample … with

“said sample” i.e., why is “said sample” stated twice? Applicants are requested to clarify.

Therefore, claims 24 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

G. For claim 26, the term “equal marker” is vague and indefinite. For example, it is not clear what “equal” refers to i.e., there is no basis for determining the equality? For example, does Applicant mean that the “markers” are “equal” because they have the same structure i.e., “equal” structures. Does Applicant mean that the “markers” the “equal” because they fluoresce with “equal” intensity or provide emit an “equal” wavelength of light? Applicants are requested to clarify. Therefore, claims 26 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

H. Claims 29-30 recite the limitation “said sample control unit.” There is insufficient antecedent basis for this limitation in the claim. Therefore, claim 28 and all dependent claims are rejected under 35 USC 112, second paragraph.

### *Claims Rejections - 35 U.S.C. 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in-

- (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
- (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

21. Claims 24-32, 34-38, 42 and 44-45 are rejected under 35 U.S.C. 102(a) as being anticipated by Steyer et al (Steyer, J.A.; Almers, W. "Tracking Single Secretory Granules in Live Chromaffin Cells by Evanescent-Field Fluorescence Microscopy" *Biophysical Journal* **April 1999**, 76, 2262-2271).

For *claim 24*, Steyer et al (see entire document) discloses materials and methods including epifluorescence microscopy for analyzing secretory granules beneath the plasma membrane of chromaffin cells (see Steyer et al, abstract), which anticipates claim 24. For example, Steyer et al discloses a least one source of light for large-area fluorescence excitation via single or multiple photon absorption by marker molecules in the sample (e.g., see Steyer et al, abstract wherein laser is discloses). Steyer et al further discloses a highly sensitive detection and analysis system comprising a charged coupled device (CCD) camera (e.g., ). Steyer et al further discloses the "microscope stage" of the epifluorescence microscope i.e., the stage of the Zeiss-Axiovert (e.g., see page 2263, column 1, Materials and Methods section). Finally, Steyer et al discloses a control unit for coordinating and synchronizing illumination times and movements of at least one of said sample (e.g., see Steyer et al, Materials and Methods, "we moved the objective lens 300 nm upward, using a calibrated piezoelectric drive; see also page 2264, column 1,

paragraph 1 wherein Steyer et al discloses a calibrated piezoelectric drive (PIFOC P-721.10; Physik Instrumente, Waldbronn, Germany) to control movements of the objective with respect to the sample).

For **claim 25**, Steyer et al discloses secretory granules and chromaffin cells (e.g., see abstract).

For **claim 26**, Steyer et al disclose green fluorescent beads (280 nm diameter) (e.g., see Figure 2).

For **claim 27**, Steyer et al discloses “marker” beads that have different fluorescent intensities (e.g., see figure 2).

For **claim 28**, Steyer et al discloses software-controlled shutter (Uniblitz; Vincent Associates, Rochester, NY) that opened only during camera exposure (e.g., see page 2263, column 2, paragraph 1).

For **claims 29-30**, Steyer et al does not explicitly state that “lateral” and “vertical” movements are coordinated but Steyer et al uses the same “epifluorescence microscope” and “normal sample holding means” as that elected by Applicant (e.g., see Paper No. 9, species election). “When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not.” *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Furthermore, Steyer et al discloses controlled vertical movements via the use of the piezoelectric device (e.g., see page 2264, column 1, paragraph 1)

For **claim 31**, Steyer et al discloses further coordinating and synchronizing positioning and shifting of images to each sample position on a pixel array of said CCD camera (e.g., see Steyer et al, Materials and Methods, "we moved the objective lens 300 nm upward, using a calibrated piezoelectric drive"; see also page 2264, column 1, paragraph 2 wherein the shutter is "coordinated" and "synchronized").

For **claims 32,34**, Steyer et al discloses an Ar<sup>+</sup> laser (e.g., see Steyer et al, figure 1).

For **claim 35**, Steyer et al discloses an Ar<sup>+</sup> laser that can generate 5 ms pulses (e.g., see Steyer et al, Materials and Methods).

For **claim 36**, Steyer et al discloses both continuous and frameshift modes (e.g., see Steyer et al, Materials and Methods; see also Image collection).

For **claim 37-38**, Steyer et al discloses an epifluorescence microscope with >3% efficiency (e.g., see Steyer et al, Materials and Methods).

For **claim 42**, Steyer et al discloses a glass slide, but any support commonly used in the field including a microtiter plate would be immediately envisioned.

For **claim 44**, Steyer et al discloses a piezo element (e.g., see Steyer et al, Materials and Methods, "we moved the objective lens 300 nm upward, using a calibrated piezoelectric drive; see also page 2264, column 1, paragraph 1 wherein Steyer et al discloses a calibrated piezoelectric drive (PIFOC P-721.10; Physik Instrumente, Waldbronn, Germany) to control movements of the objective with respect to the sample

For *claim 45*, Steyer et al discloses the same Axiovert 135-TV Zeiss microscope as that disclose in Applicant's preferred embodiments (e.g., see Example 1 in Specification) and, as a result, must possess the same parallel beam region. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

22. Claims 24-40, 42 and 45 are rejected under 35 U.S.C. 102(b) as being anticipated by Schmidt et al (Schmidt, Th; Schutz, G.J.; Baumgartner, W.; Gruber, H.J.; Schindler, H. "Imaging of single molecule diffusion" *PNAS USA* **1996**, *93*, 2926-2929).

For *claim 24*, Schmidt et al (see entire document) discloses materials and methods for single dye tracing techniques (see Schmidt et al, abstract), which anticipates claim 24. For example, Schmidt et al discloses a least one source of light for large-area fluorescence excitation via single or multiple photon absorption by marker molecules in the sample (e.g., see Materials and Methods, Fluorescence Microscopy section wherein Schmidt et al discloses Ar+ laser (Innova 306) as a "light source" and a phospholipid carrying a rhodamine dye as the "marker molecule" in a "lipid membrane" sample; see also page 2926, column 1, last paragraph; see also figure 1). Schmidt et al further

discloses a highly sensitive detection and analysis system comprising a charged coupled device (CCD) camera (e.g., see Materials and Methods, Fluorescence Microscopy section wherein epifluorescence microscope with a CCD camera; see also page 2926, column 1, last paragraph; also note that the detection system can detect a “single” molecule which makes it “highly sensitive”). Schmidt et al further discloses the “microscope stage” of the epifluorescence microscope i.e., Applicants’ elected species of holder (please note that there are many parts of the detection and analysis system that are “moveable” relative to the sample holding means e.g., see Materials and Methods disclosing “moveable” shutter for CCD). Finally, Schmidt et al discloses a control unit for coordinating and synchronizing illumination times and movements of at least one of said sample (e.g., see Schmidt et al, Materials and Methods, Fluorescence Microscopy disclosing a TH512B chip; see also page 2927, paragraph 1; see also figure 1).

For **claim 25**, Schmidt et al discloses lipid membranes and living cells (e.g., see Materials and Methods section; see also Conclusion, “one field of application is bioscience, for example, the surface of living cells”), which falls within Applicants “broad” definition for biological cells (e.g., see Specification, page 23, paragraph 1).

For **claim 26**, Schmidt et al disclose fluorescence-labeled lipids as “marker” molecules that have “equal” structures (e.g., see Materials and Methods section disclosing TRITC DHPE).

For **claim 27**, Schmidt et al discloses “marker” molecules that have different fluorescent intensities (e.g., see bell curve in figure 2 showing some “markers” with less than 100 counts and some with greater than 300 counts).

For **claim 28**, Schmidt et al discloses the coordination and synchronization of 5 ms Gaussian-shaped laser beam pulses of 6.1  $\mu\text{m}$  width and 57 kW/cm<sup>2</sup> mean excitation intensity taken at 35 ms intervals (e.g., see Figures 1,3).

For **claims 29-30**, Schmidt et al does not explicitly state that “lateral” and “vertical” movements are coordinated but Schmidt et al uses the same “epifluorescence microscope” and “normal sample holding means” as that elected by Applicant (e.g., see Paper No. 9, species election). “When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not.” *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

For **claim 31**, Schmidt et al discloses further coordinating and synchronizing positioning and shifting of images to each sample position on a pixel array of said CCD cameral (e.g., see Schmidt et al, Materials and Methods, Fluorescence Microscopy section; see also figures 1,3).

For **claims 32,34**, Schmidt et al discloses an Ar<sup>+</sup> laser (e.g., see Schmidt et al, Materials and Methods, Fluorescence Microscopy section).

For **claim 33**, Schmidt et al discloses an acoustooptic modulator (e.g., see Schmidt et al, page 2927, column 1).

For **claim 35**, Schmidt et al discloses an Ar+ laser that can generate 5 ms pulses (e.g., see Schmidt et al, Materials and Methods, Fluorescence Microscopy section).

For **claim 36**, Schmidt et al discloses both continuous and frameshift modes (e.g., see Schmidt et al, Materials and Methods, Fluorescence Microscopy section).

For **claim 37-38**, Schmidt et al discloses an epifluorescence microscope with >3% efficiency (e.g., see Schmidt et al, page 2926, column 1, last paragraph).

For **claims 39-40**, Schmidt et al discloses an N<sub>2</sub> cooled CCD with 4 counts/pixel read out noise. Furthermore, Schmidt et al discloses the AT200, which is the same CCD camera disclosed in Applicant's preferred embodiments and, as a result, must have the same properties as that claimed by Applicant (e.g., compare with the CCD camera disclosed in Example 1 of the Specification). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

For **claim 42**, any solid support commonly used in the field including a microtiter plate would be immediately envisioned by one of skill in the art.

For **claim 45**, Schmidt et al discloses the same Axiovert 135-TV Zeiss microscope as that disclosed in Applicant's preferred embodiments (e.g., see Example 1 in Specification) and, as a result, must possess the same parallel beam region. "When the

PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

23. Claims 24-32, 34-35, 37-38 and 43 are rejected under 35 U.S.C. 102(e) as being anticipated by Eriksson et al (U.S. Patent No. 6,388,746).

For **claim 24**, Eriksson et al (see entire document) discloses materials and methods for "high sensitivity" detection of fluorescent molecules (see Eriksson et al, abstract), which anticipates claim 24. For example, Eriksson et al discloses a least one source of light for large-area fluorescence excitation via single or multiple photon absorption by marker molecules in the sample (e.g., see Abstract wherein Eriksson discloses a laser including laser dyes; see column 3, line 24; see also claim 21). Eriksson et al further discloses a highly sensitive detection and analysis system comprising a charged coupled device (CCD) camera (e.g., see column 6, lines 9-10). Eriksson et al further discloses the "microscope stage" and a "three dimensional" translation stage controlled by a computer (column 15, line 6-10; see also column 11, line 53; see also column 12, line 8; column 12, line 51). Finally, Eriksson et al discloses a control unit for

coordinating and synchronizing illumination times and movements of at least one of said sample (e.g., see Eriksson et al, column 14, line 18).

For **claim 25**, Eriksson et al discloses cells (e.g., see column 1, line 24; see also column 7, line 24).

For **claim 26**, Eriksson et al disclose latex beads with approximately 100 equivalent fluorescent molecules (e.g., see Example 1).

For **claim 27**, Eriksson et al also discloses different markers that can be electrophoretically separated (e.g., see column 12, last paragraph).

For **claim 28**, Eriksson et al discloses the coordination and synchronization of 5 ms Gaussian-shaped laser beam pulses of 6.1  $\mu\text{m}$  width and 57 kW/cm<sup>2</sup> mean excitation intensity taken at 35 ms intervals (e.g., see Figures 1,3).

For **claims 29-31**, Eriksson et al discloses a computer controlled 3D stage and computer control of shutter speeds (column 15, line 6-10; see also column 11, line 53; see also column 12, line 8; column 12, line 51)

For **claims 32,34**, Eriksson et al discloses lasers like dye lasers (e.g., see abstract).

For **claim 35**, Eriksson et al discloses coordinated CO<sub>2</sub> laser pulses (e.g., see Eriksson et al, column 10, line 52).

For **claim 37-38**, Eriksson et al discloses an epifluorescence microscope with >3% efficiency (e.g., see Eriksson et al, page 2926, column 1, last paragraph).

For **claim 43**, Eriksson et al discloses a "flow through" cell (e.g., see Eriksson et al, Title, abstract; column 4, line 44; see also column 5, line 23; see also figure 8).

***Contact Information***

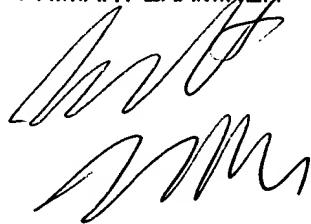
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (703) 308-2423. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (703) 306-3217. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-2439.

Jon D. Epperson, Ph.D.  
October 19, 2003

PENNELL CELSA  
PRIMARY EXAMINER

A handwritten signature in black ink, appearing to read "JON D. EPPERSO" followed by a stylized "N".